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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/734,272	12/15/2003	Yu-Fang Hu	MR929-944	1490

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EXAMINER	
KISHORE, GOLLAMUDI S	
ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
12/02/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/734,272	HU ET AL.	
	Examiner	Art Unit	
	GOLLAMUDI S. KISHORE	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 October 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,10-24 and 26-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,10-24 and 26-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The RCE dated 10-14-10 is acknowledged.

Claims included in the prosecution are 1-8, 10-24 and 26-30.

In view of the amendment to the claims, the 112, second paragraph rejection is withdrawn.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1-8, 10-24 and 26-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Slater (6,355,268) by itself or in combination with Zalipsky (6,051,251).

Slater discloses a process of preparation of liposomes. The process involves mixing soy phosphatidylcholine, cholesterol and PEG-DSPE in a mole ratio of 56. 4: 38.3: 5.3 in ethanol at 65 degrees and mixing this mixture with an ammonium sulfate solution at 65 degrees. The mixture is subjected to an extrusion process through an extruder. The ammonium sulfate and ethanol are removed from the external bulk aqueous phase prior to loading the active agent. The active agent, Topotecan is dissolved in 40 ml of 10 % sucrose solution and then remotely loaded. The method of Slater differs from instant method in that, the ammonium sulfate and ethanol are

removed by diafiltration and not by dialysis process (abstract, col. 7, line 20 through col. 9, line 23 and Example 1). One could however, interpret diafiltration as a dialysis process. Since the goal is to remove ammonium sulfate and ethanol from the liposomal mixture, it would have been obvious to one of ordinary skill in the art to use art known process of dialysis, which removes salts with a reasonable expectation of success. One of ordinary skill in the art would be motivated to use this process since the reference of Zalipsky shows the removal of ammonium sulfate from the external medium by dialysis and also equates dialysis and diafiltration for the removal of small molecular weight compounds such as drugs (Example 1 and col. 8, lines 12-16). Although Slater does not disclose claimed ranges for the individual components, since both instant invention and Slater are involved in the process of preparation of liposomes loaded with the active agents, it is deemed obvious to one of ordinary skill in the art to manipulate the amounts of the phospholipids and ethanol to obtain the best possible results. Slater does not disclose the active agent to be doxorubicin. However, since the principle of loading the active agent is the same, one of ordinary skill in the art would be able to load any active agent in the method of Slater with a reasonable expectation of success. Although Slater does not teach lyophilization of liposomes, since this step is routinely practiced in the art of liposomes, one of ordinary skill in the art would be motivated to lyophilize the liposomes with a reasonable expectation of success.

Applicant's arguments have been fully considered, but are not persuasive. Applicant argues that both Slater and Zalipsky fail to teach a suitable ratio of the alcohol solvent to the compound (i), (ii) and (iii) for increasing extrusion speed higher than 2

L/minute and lowering the extrusion pressure less than 142 psi. This argument is not persuasive since it is common knowledge that extrusion rate depends on the viscosity of the solution. This is evident also from the references cited by the examiner. The prior art is also suggestive that the amount of ethanol can be manipulated and therefore, it would have been obvious to one of ordinary skill in the art that viscosity can be reduced by increasing the amount of ethanol. The examiner also cites the reference of Edgerly-Plug (6,596,305) which teaches that certain amount of ethanol is necessary for the formation of liposomes and the amount of ethanol below this limit can be varied to obtain liposomes of specific sizes (see Abstract and entire patent). The examiner has already cited the reference of Schneider (5,393,530) which teaches the connection between the viscosity and extrusion process. On col. 7, lines 19-21 Schneider states “Also extrusion of empty liposomes is easy because of their inherent low viscosity”. This statement implies a connection between the viscosity of the solution and the extrusion process. The examiner has also cited the references of Suddith which teaches fluid viscosity affects the extrusion rate (col. 6, lines 8-14). Therefore, it would have been obvious to one of ordinary skill in the art to increase the amounts of alcohol if necessary, to reduce the viscosity of the lipid solution in ethanol such that claimed pressure can be used for extrusion process and obtain claimed speed. The examiner also cites the reference of Buckley (Us 4,434,262) which shows that the reduction in extrusion pressure an increased extrusion speed results in greater productivity. Instant invention therefore, is an obvious extension of Slater's method.

5. Claims 1-8, 10-24 and 26-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Slater (6,355,268) by itself or in combination with Zalipsky (6,051,251) as set forth above, further in view of Leigh (5,004,611) and Suddith (5,556,580).

The teachings of Slater and Zalipsky have been discussed above.

Leigh while disclosing proliposomal formulations teaches that the ratio of the lipid component to water-miscible component (ethanol) could be from 1:2 to 1:10 (abstract, col. 4, lines 35-38).

Suddith while disclosing an extrusion process of liposomes teaches that the viscosity affects the extrusion rate (col. 2, lines 52-55 and col. 6, lines 8-14).

It would have been obvious to one of ordinary skill in the art to vary the amounts of alcohol in lipid solutions of Slater to reduce their viscosity in order to facilitate extrusion at higher speed and lower pressure, if such are desired, since Leigh teaches that alcohol can be increased to 10:1 compared to the lipid amount and that of Suddith teaches that viscosity of the solution affects the extrusion rate.

Applicant's arguments have been fully considered, but are not persuasive. Applicant's arguments regarding Slater, Zalipsky, Schneider and Suddith have already been addressed by the examiner. Applicant argues that although Leigh teaches the range of the ratio of the ethanol to lipid solution, he fails to specifically teach suitable alcohol solvent ratio to compounds i, ii and iii for increasing claimed extrusion speed. This argument is not persuasive since it is within the skill of the art to realize that the extrusion pressure depends on the viscosity of the solution and thus it is a

manipulatable parameter. As indicated above, the cited prior art of interest teaches that greater productivity can be achieved by the reduction of extrusion pressure.

6. Claims 27-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Slater (6,355,268) by itself or in combination with Zalipsky (6,051,251) OR over Slater (6,355,268) by itself or in combination with Zalipsky (6,051,251) as set forth above, further in view of Leigh (5,004,611) and Suddith (5,556,580) both set forth above, further in view of Barenholz (5,316,771).

The teachings of Slater, Zalipsky, Leigh and Suddith have been discussed above. What is lacking in these references is the teaching of doxorubicin as the active agent. The use of doxorubicin as the active agent in the liposomes of Slater would have been obvious to one of ordinary skill in the art with a reasonable expectation of success since the reference of Barenholz shows the loading of doxorubicin in liposomes containing ammonium sulfate (fig. 3, examples and claims).

Applicant's arguments have been fully considered, but are not persuasive. Applicant argues that Barenholz focuses on the drug loading method in liposomes and that Barenholz never addresses the high pressure and the low extrusion speed caused during the extrusion process. This argument is not persuasive since this reference is combined for its teachings of the encapsulation of doxorubicin in liposomes and not for its teachings or lack thereof of extrusion process.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant provides no specific arguments regarding Barenholz.

5. Claims 1-8, 10-24 and 26-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Slater (6,355,268) by itself or in combination with Zalipsky (6,051,251) ,further in view of Leigh (5,004,611) and Suddith (5,556,580) as set forth above, further in view of Edgerly-Plug (6,596,305) and Buckley (4,434,262).

The teachings of Slater, Zalipsky, Leigh and Suddith have been discussed above.

Edgerly-Plug while disclosing liposomal formulations teaches that certain amount of ethanol is necessary for the formation of liposomes and the amount of ethanol below this limit can be varied to obtain liposomes of specific sizes (see Abstract and entire patent).

Buckley while disclosing melt processable blend of liquid crystalline compound and a polyester teaches that by reducing the viscosity of the blends one can reduce the extrusion pressure while extruding which in turn results in increased extrusion speed which in turn results in stable processing and longer filter pack life and greater productivity (abstract, col. 3, line 59 through col. 4, line 2, Examples and claims).

One of ordinary skill in the art would further be motivated to increase the amount of ethanol in order to obtain specific size population of liposomes as taught by Edgerly-Plug if such is desired and which in turn would decrease the viscosity of the solution to be extruded which would result in increased in viscosity speed which in turn result in greater productivity as taught by Buckley.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to GOLLAMUDI S. KISHORE whose telephone number is

(571)272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Krass Frederick can be reached on (571) 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Gollamudi S Kishore/
Primary Examiner, Art Unit 1612

GSK